High cost drugs pathway for axial spondyloarthritis in adults

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Version 1.2 (updated May 2023)

This supersedes previous Harmonised Biologics Pathway for AS and PsA (v4.2)

Review due in 2 years from publication

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DOCUMENT CONTROL

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January 2022	Authors	Draft prepared and sent out for consultation	0.1
October 2022	Anna Pracz	Consultation comments review. Alignment with other HCD pathways. Evidence updates	0.2
November 2022	Anna Pracz	Final draft for authors' review. Inclusion of updated BSR guidance on drugs in pregnancy and lactation.	0.3-0.4
December 2022	Anna Pracz	Submission to CRG and inclusion of their comments	0.5-0.6
March 2023	Anna Pracz	Correction of factual inaccuracies	1.1
May 2023	Anna Pracz	Inclusion of MHRA safety alert (JAKi) April 2023. Inclusion of NICE TA861	1.2

Approvals

This document must be approved by the following before distribution:

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GM Rheumatology working group	05.12.2022	0.5
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Distribution

Final version available on GMMMG website **http://gmmmg.nhs.uk/**

Contents

High cost drugs pathway for axial spondyloarthritis in adults

1. Background

This pathway is to be used as a guideline for axial spondyloarthritis, comprising radiographic axial spondyloarthritis (ankylosing spondylitis, AS) and non-radiographic axial spondyloarthritis. It has been written using up to date published research and evidenced based medicine. For patients with psoriatic arthritis, follow the Greater Manchester Medicines Management Group (GMMMG) High cost drugs pathway for psoriatic arthritis the GMMMG website.

Currently the pathway includes the following classes of high cost drugs (1):

- biologic DMARDs (biologic agents, biologicals)
  - tumour necrosis factor (TNF) alpha inhibitors (anti-TNFs): adalimumab, certolizumab, etanercept, golimumab, infliximab
  - interleukin-17 (IL-17) inhibitors: secukinumab, ixekizumab

- targeted synthetic DMARDs (small molecules)
  - Janus kinase (JAK) inhibitors: upadacitinib

2. NICE guidance

Biological therapies and small molecule high cost drugs are recommended as options for treating severe axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs). Additionally, British Society for Rheumatology (BSR) recommends a trial of at least two NSAIDs at the maximum tolerated dose, for at least two weeks prior to use of high cost drugs. (2)

Recommendations and product licenses differ for some high cost drugs depending on subset of axial spondyloarthritis. Notably, infliximab is not licensed for non-radiographic axial spondyloarthritis. See table 2 in section 12 for more information.

Links to the relevant NICE guidelines and technology appraisals are listed below. The NICE recommendations also apply to biosimilar products of the technologies that have a marketing authorisation, allowing the use of the biosimilar for the same indication. (3)

Any new high cost drugs that receive positive recommendation from NICE between this document iterations are approved for routine use within criteria specified in NICE technology appraisal and will be included in upcoming pathway updates.

NICE NG65 Spondyloarthritis in over 16:diagnosis and management

2.1. Biologic DMARDs

- NICE TA383 (2016): TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis
- NICE TA407 (2016): Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors
- NICE TA497 (2018): Golimumab for treating non-radiographic axial spondyloarthritis
- NICE TA718 (2021): Ixekizumab for treating axial spondyloarthritis
- NICE TA719 (2021): Secukinumab for treating non-radiographic axial spondyloarthritis

2.2. Targeted synthetic DMARDs

- NICE TA829 (2022): Upadacitinib for treating active ankylosing spondylitis
- NICE TA861 (2023): Upadacitinib for treating active non-radiographic axial spondyloarthritis

3. Initiating treatment with a high cost drug

All NICE-approved high cost drugs for treatment of axial spondyloarthritis are routinely commissioned if prescribed in accordance with this pathway and used in line with criteria in the relevant NICE technology appraisal. This includes any new high cost drugs that are approved by NICE between pathway revisions.

The choice of treatment should be guided by clinical judgement, national and local guidance, and the overall value proposition offered by the individual medicines.

Patients with axial spondyloarthritis may present with other extra-articular (inflammatory bowel disease, psoriasis or uveitis). (4) Those with concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway. See also table 2 in section 12 for drug choice.

There are further numerous factors which may influence the choice of drug at each point in the pathway, including disease presentation with activity in different domains, co-morbidities, dexterity, previous treatment history and adherence, route of administration, frequency, devices available. (5) These factors should be considered in a discussion between the patient and their clinician, including the advantages and disadvantages. The rationale for choice should be documented.

If more than one treatment is suitable, the best value product should be chosen (taking into account price per dose, dosage and treatment frequency and administration costs, and biosimilar availability). At the time of this version publication this was biosimilar adalimumab. See GMMMG (2016): Prescribing of high cost biosimilar biological medicines. Clinicians should also contact pharmacy for advice on the relative cost-effectiveness of these drugs. If the least expensive product is not prescribed, the reasons why must be documented made available to commissioners if requested. Records can be made on Blueteq forms where applicable.

In line with the MHRA guidance (2008): Biosimilar products, biologics including biosimilars must be prescribed by brand name (i.e. the brand of biosimilar or originator product) to support ongoing pharmacovigilance of the individual products.

Pharmacovigilance is essential for any new high cost drug medicine (including biosimilars and newer classes of drugs, e.g. JAK inhibitors) and additional monitoring is indicated through the MHRA's Black Triangle Scheme.

Patients should be enrolled on to the relevant registry which serves data collection on the safety and effectiveness of medicines in clinical practice. See section 11 for more on registries.

Treatment should be reviewed initially to assess efficacy at 3-6 months as per British Society of Rheumatology (4) (6) (5). NICE specifies explicitly timing for review for individual high cost drugs (12-20 weeks, see sections 2 and 12). For treatment pathways, see flowcharts in section 13. For specific treatment selection criteria table 2 in section 12 lists available treatments.

4. Biosimilars

Use of biosimilars, including switching from originator to a biosimilar, has become routine clinical practice. All NICE guidance on biologics applies to biosimilar medicines. The British Society for Rheumatology (BSR) have published a biosimilar position statement which states:

- When considering switching patients on a biologic originator product to a biosimilar, patients must be provided with sufficient information to make an informed decision, with the support of their rheumatology multidisciplinary team.
- No patients should be switched from one biosimilar to another biosimilar of the same originator product purely based on cost, as there are potential concerns over patient safety and immunogenicity.
- When the specific biologic prescribed is unavailable, the dispensing pharmacist must contact the prescribing clinician to seek advice as to appropriate short-term alternatives. The patient must be always informed about any discussions concerning their medicine.

Furthermore, the GMMMG advised in its statement on biosimilar, regarding changing from originator to a biosimilar (3):

- There is evidence that patients who are in a stable clinical response or remission may be changed over to the biosimilar at the same dose and dose interval. This should be done after discussion and agreement with individual patients.
- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing and in discussion with the hospital pharmacy department.
- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing.

N.B. Inflectra® and Remsima® are different brands of infliximab and are marketed by different companies, but it should be noted that they are the same biosimilar (CPT-13, produced by the same manufacturer, Celltrion).

5. Alternative dosing of high cost drugs (including dose escalation and de-escalation)

Treatment optimisation, including dose escalation, and de-escalation, is licensed for several drugs (1).

For treatment initiation refer to individual drug's SPC via https://www.medicines.org.uk/.

For some drugs, reduced doses are indicated in the elderly, renal impairment, hepatic impairment and according to blood test results – see section 19 for specific monitoring considerations and summary of product cha4acteristics for adjusted dosing. For safety alerts recommending dose adjustments see section 15.

Patients with axial spondyloarthritis may present with other extra-articular (inflammatory bowel disease, psoriasis or uveitis). (4) Those with concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway. See also table 2 in section 12 for drug choice.

Table 1. Standard and alternative HCD regimens (1)

Drug	Standard maintenance dose	Alternative regimes
Adalimumab (SC)	40mg every two weeks	Not specified in the marketing authorisation
Certolizumab pegol (SC)	200mg every 2 weeks	400mg every 4 weeks once clinical response is confirmed. After at least 1 year of treatment, in patients with sustained remission, a reduced maintenance dose of 200mg every 4 weeks may be considered
Etanercept (SC)	50mg once weekly	25mg twice weekly
Golimumab (SC)	50mg monthly	100mg monthly, in patients >100kg who do not achieve an adequate response on 50mg monthly after 3-4 doses
Infliximab (IV)*	5mg/kg every 8 weeks	5mg/kg every 6 weeks if response not achieved on 5mg/kg every 8 weeks, based on adequate response with drug and/or antibody levels if available and appropriate
Ixekizumab (SC)	80mg every 4 weeks	Not specified in the marketing authorisation
Secukinumab (SC)	150mg monthly	For radiographic ankylosing spondylitis only, based on clinical response the dose can be increased to 300mg monthly
Upadacitinib ** (PO)	15mg once daily	Not specified in the marketing authorisation

IV – intravenous; PO - oral; SC – subcutaneous

*Infliximab is not licensed in non-radiographic axial spondyloarthritis and does not have NICE approval in this indication. It is included in this pathway for use in radiographic axial spondyloarthritis.

** Upadacitinib for non-radiographic axial spondyloarthritis is under NICE appraisal at time of writing

In sustained remission, tapering of biologic agents should be considered. (4) .

6. Treatment failure with a high cost drug

Although many patients initially respond well to fist-line treatment, they may subsequently lose response. A proportion of patients also do not respond to the chosen treatment at all. For those non-responders, as well as in patients where drug needs to be discontinued as described below, switching therapy is required to achieve and maintain treatment targets. (5) For the purposes of this pathway, this can include failure due to inefficacy:

- Primary failure: the axial spondyloarthritis does not respond adequately to a high cost drug within the timescales defined in the marketing authorisation and NICE technology appraisal (see section 2)
- Secondary failure: the axial spondyloarthritis initially responds adequately within the timescales defined in marketing authorisation and NICE technology appraisal (see section 2), but the patient subsequently loses this response. Although all high cost drugs are highly efficacious in the short term, longer-term attrition is observed. In effect, changes to therapy may be required for longer term disease control for a life-long condition.

There may be other reasons for treatment discontinuation, including:

- adverse effects resulting in reduced tolerability
- newly identified drug safety issue during successful treatment resulting in a newly identified relative or absolute contraindication
- patient becoming pregnant (see section 17.2)

7. Sequential use of high cost drugs

Prior to switching to a subsequent treatment, consideration may be given to dose escalation where there is evidence to support safety and efficacy (see section 5), and when an inadequate primary response may be due to insufficient drug dosing. For example, in obese patients or when disease relapses during the treatment cycle.

Degree of response or lack of response to one high cost drug is not predictive of a patient's likely response to alternative agents in an alternative class, or even in the same class. (7)

High cost drugs currently available for axial spondyloarthritis have different molecular targets (e.g. TNFα, IL-17, JAK), or have varying affinity or avidity where the target is the same. Using an agent with a different mechanism of action to the failed therapy may result in regaining disease control.

Choice of subsequent agent should be made following review by a specialist with consideration given to the mechanism of action of previously used drugs, the severity and current level of disease control, the presence of co-existing conditions, as well as the patient's past medical history and with regards to contraindications and precautions to available treatment options. This should be a shared decision with the patient. See section 3 for more details on factors to consider when initiating treatment with a new high cost drug.

In complex cases, it is recommended to seek advice from other professional colleagues, e.g. as a part of multi-disciplinary team discussion. Where available, specialist pharmacist should be involved in decision making.

With each new treatment, patients must meet the criteria laid out in the relevant NICE technology appraisal or otherwise stipulated in this pathway. There is no need for an individual funding request in such circumstances.

Recommendations differ on the need for a washout period when switching from one high cost drug to another. There are very little published data on this topic. The following should be considered when switching: clinical circumstances, drug levels (where appropriate), half-life of the drug (table 3 in section 16), safety (e.g. bridging with steroids) and practical considerations. The next drug could be started when the previous drug was due next dose or at least after one-half life of current drug has passed (whichever is longer).

Switching to a biosimilar of successful treatment (e.g. as a part of switching programme) is not considered a sequential high cost drug use.

Repeated pre-high cost drug checks should be considered when switching to a new agent as per clinical judgement, and depending on the duration of previous therapy, the clinical picture of individual patient and relevant risk factors.

8. Data collection requirements

Patient-level information including full clinical details, e.g. disease scores at treatment initiation and assessment for continuation, previous drug history, reasons for change of treatment must be made available to commissioners. This is expected to be via Blueteq or equivalent, where commissioned.

Where available and subject to contractual arrangements Blueteq or equivalent forms which comply with this pathway should be filled in for each new high cost drug at initiation and continuation to secure funding.

Where agreed, data available from Blueteq (or equivalent) system or clinical audit may be used to monitor compliance with NICE and GMMMG pathway and for other purposes (e.g. service development or pathway extension for newly identified cohorts of patients).

9. Individual funding requests (IFR)

Individual funding request will be considered under the GM EUR Operational Policy.pdf (gmeurnhs.co.uk).

Exhausting the treatment options in this pathway does not automatically establish exceptionality.

10. Free of charge schemes

All free of charge schemes must be approved in accordance with trust guidance and the GMMMG Free of Charge guidance. (8) Approval should be agreed at the trust's medicines management committee.

There must be clear exit criteria that do not place financial burden on commissioners and do not raise patient's expectations of continuation of treatment.

11. Research

Where available, enrolment in a suitable registry or observational clinical trial is encouraged so that specific information about these treatments in axial spondyloarthritis can be captured.

Clinicians are strongly encouraged to participate in long-term safety studies or registries such as BSRBR-AS (no longer recruiting patients). For more information visit www.rheumatology.org.uk/practice-quality/registers/ankylosing-spondylitis. In addition, opportunities for local observational research studies may also be considered.

Some sites host early and later phase clinical trials of novel high cost drugs. Active trials can be found on the NIHR website.

12. Available drugs and factors affecting drug choice

Where multiple treatment options are clinically suitable the best value drug, all factors considered, should be chosen. See section 3 for considerations regarding new drugs initiation.

Patients with axial spondyloarthritis may present with other extra-articular (inflammatory bowel disease, psoriasis or uveitis). (4) Those with concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway. See also table 2 below.

Note that all bDMARDs and JAK inhibitors may increase infection risk. Consider oral or intravenous options if needle phobia or inability to self-administer subcutaneous injections; intravenous preparations may help address adherence issues, or severely impaired manual dexterity. For safety alerts on safety of JAK inhibitors see section 14.

Abbreviations

BASDAI - Bath Ankylosing Spondylitis Disease Activity Index
JAK inhibitors – Janus kinase inhibitors (baricitinib, et
VTE/PE – venous thromboembolism /pulmonary embolism
bDMARD – biological DMARD (adalimumab, etc)
TB – tuberculosis
HCD – high cost drug
UC – ulcerative colitis

Table 2. Available HCDs – information to support choice

Drug & route of administration	Mode of action	Radiographic ankylosing spondylitis	First line?	Non-radiographic axial spondyloarthritis	First line?	Initial review	Other regulatory, licensing and safety considerations For patients with dactylitis, enthesitis, or nail psoriasis see GM HCD Pathway for psoriatic arthritis via the GMMMG website
Adalimumab (SC)	TNF-inhibitor	TA383	Yes	TA383	Yes	12 weeks	Licensed & NICE-approved in psoriasis (TA146), Crohn's (TA187), UC (TA329), hidradenitis suppurativa (TA392), uveitis (TA460)
Certolizumab pegol (SC)	TNF-inhibitor	TA383	Yes	TA383	Yes	12 weeks	Consider first line in women who are pregnant or breastfeeding, or who are likely to become pregnant during treatment (1) (9) NICE-approved in psoriasis (TA574). Licensed in US (but not UK) for Crohn's (Cochrane). Some evidence for efficacy in uveitis (10), but no UK licence.
Etanercept (SC)	TNF-inhibitor	TA383	Yes	TA383	Yes	12 weeks	NICE-approved in psoriasis (TA103), but not in GMMMG psoriasis pathway due to lower efficacy. Consider if anti-TNF is otherwise appropriate, but patient at risk of TB or has potential serious infection risk or previous hospitalisation for infection while on anti-TNFs (6) (11)
Golimumab (SC)	TNF-inhibitor	TA383	Yes	TA497	Yes	12 weeks	NICE-approved in UC (TA329). **NB: not licensed for psoriasis.** Consider for use in patients weighing >100kg (higher dose licensed in this population).
Infliximab (IV)	TNF-inhibitor	TA383	Yes	Not licensed*	Yes	12 weeks	NICE-approved in psoriasis (TA134), Crohn's (TA187), UC (TA329). Some evidence for efficacy in uveitis (6) (12) but no UK licence. *Infliximab is not licensed in non-radiographic axial spondyloarthritis and does not have NICE approval in this indication.

Drug & route of administration	Mode of action	Radiographic ankylosing spondylitis	First line?	Non-radiographic axial spondyloarthritis	First line?	Initial review	Other regulatory, licensing and safety considerations For patients with dactylitis, enthesitis, or nail psoriasis see GM HCD Pathway for psoriatic arthritis via the GMMMG website
Ixekizumab (SC)	IL-17 inhibitor	TA718	2nd line*	TA718	2nd line*	16-20 weeks	NICE-approved in psoriasis (TA442). *only if anti-TNF failed or not suitable
Secukinumab (SC)	IL-17 inhibitor	TA407	Yes	TA719	2nd line*	16 weeks	NICE-approved in psoriasis (TA350). *only if anti-TNF failed or not suitable
Upadacitinib (PO)	JAK inhibitor	TA829	2nd line*	TA861	2nd line*	16 weeks	NICE-approved UC (TA856) *only if anti-TNF failed or not suitable

13. GM High cost drugs pathway for axial spondyloarthritis

Active axial spondyloarthritis (BASDAI and spinal VAS ≥4) despite NSAIDs (2)

At all stages when treating with high cost drugs

- Consider entry to a trial or registry (where criteria are met)
- Review applicable patient, disease, and drug factors, e.g., dexterity, adherence, comorbidities, weight, drug history, family planning, risk of infection, route of administration, device, and dose frequency
- See section 19 for high cost drug screening questions for pre-admission.

First line (HCD-naive): choose based on clinical factors and best value.
For more details see section 12 and purple box to the right

Review at 3-6 months (2), and as per NICE guidance (see section 2)

Adequate response

- BASDAI reduction of ≥50% or ≥2 units, plus reduction in pain VAS of ≥2 cm, **and**
- treatment tolerated

Continue treatment
Review every 6 months (2)

Continued response
If a patient is in sustained remission, tapering of a bDMARD can be considered. (4)

Inadequate response
Consider potential factors that could be addressed including confirming correct diagnosis, adherence, pain due to other causes, drug levels and immunogenicity.

Secondary failure

- Loss of response or disease worsening
- Emerging adverse drug reactions

Optimise dose prior to switching, if possible. Review patient factors as described above.

Primary failure
Criteria for adequate response not met within timescales defined by NICE

Choose alternative high cost drug

- Following a high cost drug failure, consider switching to another bDMARD (anti- TNF or IL-17i) or a JAK inhibitor.
- Consider domains of disease, previous medication use, pain due to other causes, drug levels, immunogenicity
- See purple box to the right and table 2 in section 12 for choice

Therapeutic drug monitoring (adalimumab/infliximab)

- Target adalimumab drug trough level ≥ 5 mcg/mL (suggest aim: 5-10 mcg/mL)
- Target infliximab drug trough level = 7-10 mcg/mL

Drug levels low /undetectable and ADAb -ve

- Check adherence
- Increase drug dose or frequency
- Add in cDMARD

Drug levels low /undetectable and ADAb +ve
Potential loss of response.

- Add in cDMARD
- Switch to another anti-TNF*
- Swap to non-anti-TNF or JAK inhibitor

Drug level within or above range/ ADAb +/-ve and clinical loss of response
Likely non-TNF driven disease.
Switch to:

- non-anti-TNF
- JAK inhibitor

*Consider etanercept if not already used as considered less immunogenic (20) or appropriate alternative (if ADAb levels allow)

Anti-TNF drug level & antibodies undetectable -assess adherence, increase drug dose and frequency if appropriate – see section 5. Consider BMI: Is dose weight-adjusted? If adjustments do not result in adequate response, consider switching to alternative bDMARD or JAK inhibitor. See section 12 for choice.

- **For peripheral disease consider:** Anti-TNF, IL17 and JAKi (upadacitinib)
- **For psoriasis consider:** Monoclonal anti-TNF, IL17
- **If moderate/severe or recurrent uveitis consider:** Adalimumab, certolizumab, infliximab
- **If Crohn's disease consider:** Adalimumab, infliximab, certolizumab
- **If ulcerative colitis consider:** Adalimumab, infliximab, golimumab

14. Contraindications, special warnings and precautions

14.1. Cautions and contraindications

Cautions, contraindications, and special warnings regarding use of systemic agents for axial spondyloarthritis are detailed in the individual summaries of products characteristics (SPCs), which are available from www.medicines.org.uk. Prescribers should consult the relevant SPC to inform clinical decision-making for individual patients, which is beyond the scope of this guideline. . For further guidance, see the BSR biologic DMARD safety guidelines in inflammatory arthritis (2019) or most up to date guidance.

It is important that clinical teams regularly identify patient cohorts affected by new and existing safety alerts. Review of appropriateness of continuing or changing treatment should be assessed on case-by-case basis and allowing shared decision making.

14.2. Additional safety considerations

The MHRA has published Drug Safety Updates relating to several of the drugs included in this pathway. Visit www.gov.uk/drug-safety-update for up to date information on safety issues.

- Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious **infections,** and increased mortality (2023).
  In clinical trials of patients with RA, an increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality, was observed in patients treated with some JAK inhibitors, particularly tofacitinib, when compared to those treated with anti-TNFs.
  - It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current or past long-term smoking and other risk factors for cardiovascular disease or malignancy.
  - JAK inhibitors should be used in caution if prescribing in patient with any risk factors for VTE. Lower doses should be use where specified the individual summaries of products characteristics.
  - Incidence of non-melanoma skin cancer was higher in tofacitinib trials when compared with anti-TNFs. Therefore, periodic skin examinations for signs of skin malignancy is recommended in all patients on JAK inhibitors. Inform patients of these risks and key signs and symptoms that could warrant urgent medical attention.

  As indicated in 15.1, appropriateness of continuing or changing treatment in the context of the above guidance should be assessed on a case-by-case basis and with shared decision making.

- Live attenuated vaccines: avoid use in those who are clinically immunosuppressed; 2016
- Tumour necrosis factor alpha inhibitors; 2014. Risk of tuberculosis - screen all patients before starting treatment and monitor them closely.

In November 2022, the European Medicines Agency published results of review of the safety of JAK inhibitors. The recommendations include restricting use of these drugs in some patient groups to reduce the risk of serious side effects with JAK inhibitors. The MHRA has said it will look at safety measures around use of JAK inhibitors. (13) Until then clinical judgement is necessary to determine best drug choice for individual patient.

14.3. Malignancy

The use of rheumatology high cost drugs in patients with a history of malignancy should involve a detailed discussion with the patient around the risks and benefits of treatment and consideration should be given to involving their oncologist. If a cancer occurs during treatment with a high cost drug, oncologist advise on treatment might be sought.

15. Pre-high cost drug screening

Please refer to the checklist provided at the end of the document (section 19), which can be adapted locally if necessary.

15.1. Tuberculosis (TB)

Interferon gamma (gIFN) testing is recommended prior to commencing biologic, JAK inhibitor or other small molecule high cost drug if available. Parts of Greater Manchester are identified as areas of high-risk for tuberculosis. In patients with high index of suspicion or risk of tuberculosis consider referring to previously published algorithms for additional screening (14) and refer for a respiratory opinion if deemed necessary: See NICE guideline NG33, Tuberculosis (Sept 2019) for further information.

With anti-TNF therapy, risk of TB reactivation appears lowest in etanercept compared to monoclonal antibodies (infliximab and adalimumab). (6) There also appears to be a signal of concern from clinical trials with newer monoclonal antibodies such as certolizumab and golimumab, however data from observational studies is currently lacking. (6)

15.2. Hepatitis B & C

Screening for hepatitis B and C is recommended for all patients starting a biologic and JAK inhibitors or other small molecule high cost drug. BSR guidance recommends that screening should include: (6)

- Hepatitis B: screen for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc, HBcAb), followed by HBV DNA test if HBsAg or anti-HBc are positive.
- Hepatitis C: screen for anti-hepatitis C antibodies. If test is positive, hepatitis C RNA or core antigen assays should be performed.

If either hepatitis B or hepatitis C infection is suspected, discuss with a hepatologist. Treatment with a biological DMARD may be appropriate but should follow a risk/benefit decision made with a hepatologist, infectious disease or another relevant specialist.

15.3. Human immunodeficiency virus (HIV)

Screening for HIV is recommended for all patients starting a rheumatology high cost drug. NICE Quality Standard QS157 recommends young people and adults are offered an HIV test when admitted to hospital in areas of extremely high HIV prevalence, or when having a blood test when admitted to hospital in areas of high HIV prevalence. Greater Manchester is an area of high and extremely high HIV prevalence. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis recommends risk factors for HIV infection should be documented prior to commencing a high cost drug and, if present, an HIV test should be performed. If considering the use of a high cost drug in HIV positive patients, this should be discussed with an HIV specialist.

16. Surgery and perioperative risk

Potential benefit of reduced risk of post-operative infections by stopping treatment should be balanced against risk of flare in disease activity. For most treatments consideration should be given to planning surgery when at least one dosing interval has elapsed for that specific drug. (6)

For higher risk procedures consider stopping 3–5 half-lives (if this is longer than one dosing interval) before surgery. In all cases, rheumatology consultant should be involved.

High cost drugs should be recommenced after surgery when there is evidence of good wound healing (typically around 14 days), all sutures and staples are out, and there is no evidence of infection. For further guidance, see The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis or review trust's perioperative guidelines if applicable.

Table 3. Peri-operative supportive information (1) (6) (15)

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last drug dose administered)	One mean half-life	Five half-lives
Adalimumab	Every 2 weeks	Week 3	14 days	70 days
Certolizumab pegol	Every 2 weeks Every 4 weeks	Week 3 Week 5	14 days	70 days
Etanercept	Weekly or twice weekly	Week 2	3 days	15 days
Golimumab	Every 4 weeks	Week 5	14 days	70 days
Infliximab IV	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9 days	45 days
Ixekizumab	Every 4 weeks	Week 5	14 days	70 days
Secukinumab	Every 4 weeks	Week 5	30 days	150 days
Upadacitinib	Once daily	Day 4**	14 hours	3 days

*No published guidance available, recommendation based on half-life (1) or dosing interval (6).
**Another JAK inhibitor, tofacitinib is rapidly eliminated but treatment effects do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the half-life (1). Although not stated in summary of product characteristics this may be applicable to all JAK inhibitors due to mechanism of action. Prescribers may wish to consider longer time to surgery, i.e. Week 2.

17. Fertility, pregnancy and lactation

Prescribers should be mindful that evidence base evolves and to use the most up to date national guidance if in doubt. At the time of writing, the BSR pregnancy and breastfeeding guideline renewed in October 2022 was based on most up to date evidence and should be referred to in first instance. Where data is not available (e.g. for newer drugs), manufacturers' recommendations may be taken into consideration.

17.1 Fertility and conception

Medicines included in this pathway may affect fertility and conception. Women of childbearing potential should use effective contraception during treatment and continue use for the number of weeks after treatment has stopped (see table 4 in section 17.2). **Paternal exposure to high cost drugs included in this pathway is compatible with pregnancy.** (16)

When giving family planning advice, the clinician should consider the half-life of the drug in use, advice on length of contraception after the last dose, and existing evidence for use in pregnancy and breastfeeding.

17.2. Pregnancy

Among biologics, anti-TNFs, can be considered during pregnancy. The BSR (16) advise that:

- Women stable on anti-TNF therapy with known placental transfer (adalimumab, infliximab, golimumab) do not need to be switched to an anti-TNF with established minimal placental transfer (certolizumab) before or during pregnancy.
- Certolizumab due to no to minimal rate of transplacental transfer, can be considered for use thorough pregnancy.
- Patients who stop anti-TNF therapy during pregnancy may, if needed, be re-loaded as soon as possible after delivery to manage maternal disease, given infection or other complications of postpartum are excluded, and regardless of breastfeeding status.
- Lower grade, limited evidence is available for IL-17 and IL-12/23 inhibitors and is insufficient to recommend for use in pregnancy, unless there are no alternatives to control severe disease.
- JAK inhibitors are contraindicated and should be stopped at least two weeks before conception and should not be used during breastfeeding.

No studies for upadacitinib were identified in the guidance review.

The decision to continue treatment in pregnancy needs to be individualised, considering all relevant factors (e.g. alternative therapies, the severity of the mother's condition prior to therapy, the risk of a disease flare caused by cessation of therapy, and the impact of a flare on the mother and the unborn child). This should be discussed by a multi-disciplinary team.

The following table contains advice from BSR and lists manufacturers' recommendations on time to continue contraception after treatment cessation and compatibility with pregnancy trimesters.

For stopping biologics in pregnancy to enable infant vaccinations per UK schedule see section 17.4.

Table 4. Peri-conception and pregnancy compatibility

Drug	Time to continue contraception after treatment cessation [SPCs] (1)	Compatibility with trimesters [BSR 2022] (16)		
		Peri- conception	First	Second/ Third
Adalimumab	5 months	Yes	Yes	Yes
Certolizumab	5 months	Yes	Yes	Yes
Etanercept	3 weeks	Yes	Yes	Yes
Golimumab	6 months	Yes	Yes	Yes
Infliximab	6 months	Yes	Yes	Yes
Ixekizumab	10 weeks	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Secukinumab	20 weeks	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Upadacitinib*	4 weeks	Stop ≥2 weeks pre-conception	No	No

* However, as effects of JAK inhibitors may persist after drug elimination, a waiting period of one menstrual cycle before conception is advised.

** May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable.

Further information to support decision-making is available from:

- BSR guidance on prescribing of drugs in pregnancy and lactation
- Summaries of product characteristics (www.medicines.org.uk)
- UK Teratology Information Service (UKTIS) at https://uktis.org or 0344 892 0909 (Monday-Friday, 9am-5pm).

Exposures in pregnancy should be reported to UKTIS by use of their online reporting form (https://uktis.org/surveillance/reporting-an-exposure-in-pregnancy/). UKTIS are commissioned by the UK Health Security Agency (formerly Public Health England) to perform national surveillance of known and emerging human teratogens across the UK.

Advice and risk assessment for individual patients may also be available by contacting a local medicines information service via hospital pharmacy departments.

17.3. Breastfeeding

Biologics in general, and in particular anti-TNFs, are considered compatible with breastfeeding. The BSR (16) advise that:

- Anti-TNFs are compatible with breastfeeding.
- Based on limited evidence, non-anti-TNF biologics are compatible with breastfeeding (but note no data on guselkumab and risankizumab to date).
- JAK inhibitors should be avoided in breastfeeding.
- No data for apremilast to date.

Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot always be excluded. A decision on whether to breastfeed and continue or discontinue therapy should be made considering the benefit of breastfeeding to the child and the benefit of woman.

Further information to support decision-making may be available from:

- BSR guidance on prescribing of drugs in pregnancy and lactation
- Specialist Pharmacy Service (SPS) website at www.sps.nhs.uk
- Summaries of product characteristics (www.medicines.org.uk)
- Local medicines information service via hospital pharmacy departments.

17.4. Vaccination of infants exposed to drugs due to maternal treatment

Immunisation schedules in infants after in-utero exposure to biologics will depend on timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and live vaccine. (16) The BSR recommend that:

- Women considered to have low risk of disease flare on withdrawal of anti-TNF in pregnancy could stop infliximab at 20 weeks, adalimumab and golimumab at 28 weeks and etanercept at 32 weeks so that a full-term infant may receive the normal UK vaccination schedule, including rotavirus vaccine at 8 weeks.
- Adalimumab, etanercept, infliximab or golimumab may be continued throughout pregnancy, to maintain disease control. In such case, immunisation with live vaccines should be avoided until infants are 6 months of age.
- Exposure to certolizumab in utero does not require any changes to vaccination schedule.

Table 5. Pregnancy exposure and impact on infant live vaccines schedule (16)

Drug	Pregnancy exposure and impact on infant live vaccines schedule
Adalimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Certolizumab	No adjustment to vaccination including live vaccines needed.
Etanercept	If stopped by 32 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Golimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Infliximab	If stopped by 20 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.

Drug	Pregnancy exposure and impact on infant live vaccines schedule
Ixekizumab	If used to treat severe maternal disease in the third trimester, avoid all live vaccines in the infant vaccination schedule until 6 months of age.
Secukinumab	If used to treat severe maternal disease in the third trimester, avoid all live vaccines in the infant vaccination schedule until 6 months of age.
JAK inhibitors	Not applicable. Contraindicated in pregnancy.

The live vaccinations currently included in the childhood vaccination schedule for infants aged <1 year are: (17)

- BCG for tuberculosis – variation across the country depending on incidence of TB. Some areas of GM are considered to have high incidence. Isolated cases of neonates who died from disseminated BCG vaccination or TB infection after exposure to an anti-TNF medicine in utero were reported to MHRA. they were probably not known to be immunosuppressed at the time of vaccination. (18) The BCG vaccine may easily be deferred to be given later in life. (16)
- Rotavirus - all infants. Rotavirus is the most common cause of gastroenteritis in infants in the UK. The rotavirus course of vaccination must be completed by 24 weeks of age due to risk of intussusception. (17) Although there is limited evidence of safety and efficacy in infants with immunosuppression, vaccination of infant exposed in utero may be considered following careful consideration of the risks and benefits and following specialist consultation.

For advice on other live vaccinations following exposure to biologics in breastmilk, healthcare professionals should contact the relevant specialist for advice.

If there is any doubt as to whether an infant due to receive a live attenuated vaccine may be immunosuppressed due to the mother's therapy, including exposure through breast-feeding, specialist advice should be sought. (19)

Current vaccination strategies with non-live vaccines for infants who have been exposed to biologic medicines *in utero* do not differ from those for unexposed infants.

18. Vaccinations

Where possible, vaccination requirements should be reviewed and brought up to date prior to initiation of high cost drug therapy, with reference to Department of Health Guidance. (19) (17) During high cost drug therapy, patients should receive (inactivated) influenza vaccine annually and pneumococcal vaccine once only. For vaccination of infants see section 17.4.

18.1. Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents and cautioned in patients on JAK inhibitors. It is safe to administer a live vaccine 4 weeks prior to commencing biologic or tofacitinib therapy, when necessary. There is no contraindication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs.

When a live vaccine is required by a patient on a high cost drug, stopping treatment (following careful assessment of the risks and benefits) may enable a necessary vaccination to be administered. The decision to vaccinate should be guided by the drug half-life (see table 3 in section 17). For further relevant summaries of products characteristics, www.medicines.org.uk

- the Green Book, https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book (19)
- Specialist advice

The table below shows all live vaccines available in the UK.

Table 6. Live vaccines available in the UK

Live vaccine	Brand name
Tuberculosis - BCG	Bacillus Calmette-Guerin Vaccine
Influenza (nasal)	Brand can change yearly in the UK
Measles, mumps and rubella combined vaccine (MMR)	MMRvaxPRO®, Priorix®
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster vaccine	Varilrix®, Varivax®, Zostavax®
Yellow fever	Stamaril®

18.2. Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on high-cost therapies, though they may elicit a lower response than in immunocompetent individuals.

Non-live vaccines should be given 2-4 weeks before starting immunosuppressant therapy, as response after starting treatment can be poor.

For information on specific vaccines please refer to the appropriate Summary of Product Characteristics (www.medicines.org.uk) or the Green Book: Immunisation against infectious disease. (19)

For information on COVID-19 vaccines please refer to the Green Book: Immunisation against infectious disease Chapter 14a.

Shingrix® a non-live vaccine for varicella zoster virus (VZV) is now available in the UK. From 2021, individuals who are eligible for shingles vaccine (adults aged 70-79 years), but who are contra-indicated to the receipt of the live vaccine should be offered Shingrix® instead. Adults should receive two doses of Shingrix® a minimum of 2 months apart. For more information please refer to the Green Book: Immunisation against infectious disease Chapter 28a (19)

19. Checklist for patient screening on selection for high cost drug agents

Screening investigations requested in clinic				
		Y/N	**Initial**	**Results/Details**
FBC/U&E/LFT/ESR/CRP				
ANA *(If positive also order ENA/dsDNA/C3/C4)*				
HIV, HBV *(surface antigen, core antibody)* *, **HCV** *(antibody test) If positive result please refer to hepatology/GUM/ID as relevant* * Reactivation has been reported in HBsAg-ve as well as HbsAg +ve patients stressing the importance of measuring not only HbsAg but also antibodies against HBc antigen to identify positive carrier status				
Varicella zoster IgG (If negative inform GP and patient)				
TB screening *(g-IFN testing)* *If positive refer to respiratory*				
Chest X-ray *(within the last 6 months)* *(± pulmonary function tests/HRCT thorax)* **CXR checked by/date**				
Additional monitoring: JAK inhibitors	**Fasting lipids** (if abnormal treat according to local guidelines)			
Screening questions asked in clinic				
		Y/N	**Initial**	**Details**
Previous TB/TB contact (*details*)				
Travel abroad since last review *(i.e., TB/viral hepatitis high risk countries)* *Which country/Dates*				
History of heart failure (NYHA class III or IV) *(details)*				
History of recurrent infection *(details)*				
History of interstitial lung disease *(details such as extent of ILD)*				
History of cancer/malignancy *(Type/Date when occurred/Date of all clear)*				
Date of last mammogram (50yr +) *(encourage patient to visit GP if >3 years)*				
Date of last smear (25yr +) *(encourage patient to visit GP if >3 years)*				
History of allergy/infusion reaction to any agent *(to what/type of reaction)*				
History of cardiovascular risk factors				
History of thrombotic event (e.g. DVT/PE)				
Any live vaccinations in the last 4 weeks				
History of demyelinating disease *(details)*				
History of diverticular disease *(details)*				
Concurrent immune disease (e.g. uveitis, IBD, psoriasis)				
Education				
Pregnancy/breastfeeding advice given				
Vaccination advice given				
Patient counselled and educated				
Patient consent to be approached for research				

20. Specific monitoring considerations

See screening questionnaire (section 19) for full details of baseline monitoring that should be performed in all patients considered for high cost drugs.

Ongoing monitoring in line with BSR guidance is recommended for all patients, e.g. FBC, creatinine/calculated GFR, ALT/AST and albumin every 3-6 months. (6)

Additional monitoring is recommended for some biologics and for the JAK inhibitors, as described below.

20.1. Upadacitinib

MHRA: Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections, and increased mortality (2023). It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current, or past long-time smoking and other factors for cardiovascular disease or malignancy.

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (1)		
Recommended monitoring	• Check FBC at baseline and then no later than 12 weeks after initiation of treatment	
Recommended actions	**ALC** (laboratory value: 10^9 cells/L)	
	ALC > 0.5	Continue treatment
	ALC <0.5	Interrupt treatment. Restart once ALC >0.5.
	ANC (laboratory value: 10^9 cells/L)	
	ANC >1.0	Continue treatment
	ANC <1.0	Interrupt treatment. Restart once ANC >1.0.
	Haemoglobin (laboratory value: g/dL)	
	Hb >8	Continue treatment
	HB <8	Interrupt treatment. Restart once Hb >8
Hepatic transaminases		
Recommended monitoring	• Check hepatic transaminases at baseline and thereafter according to routine management	
Recommended actions	• Temporarily interrupt treatment if drug-induced liver injury is suspected	
Lipid parameters		
Recommended monitoring	• Lipid parameters should be assessed at baseline and repeated after 12 weeks.	
Recommended actions	• Treat any lipid abnormalities in line with local practice.	
Renal impairment		
Recommended actions	• No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment. Upadacitinib 15 mg once daily should be used with caution in patients with severe renal impairment.	
Age considerations		
Recommended actions	• Only use in patients aged 65 years and older if no suitable alternative (no dose adjustment). • There are limited data in patients 75 years of age and older.	
Other safety considerations (MACE, VTE, malignancy)		
Recommended monitoring	• Patients should be re-evaluated periodically during baricitinib treatment to assess for changes in VTE risk. • Promptly evaluate patients with signs and symptoms of VTE and discontinue baricitinib in patients with suspected VTE, regardless of dose or indication. • Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.	
Recommended actions	• No dose adjustment.	

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